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Prehospital synergy: Tranexamic acid and blood transfusion in patients at risk for hemorrhage

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Author Contributions

APD, LH, JBB participated in the literature search. APD, JBB participated in the study design. APD, JBB participated in the data collection. APD, JBB participated in the data analysis. All authors participated in data interpretation. APD, LH, SL, JBB participated in the writing of the manuscript. All authors participated in the critical revision of the manuscript for important intellectual content.

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SUPPLEMENTAL DIGITAL CONTENT

Supplemental Methods

eFigure 1

eTable 1

eTable 2

Supplemental References

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Abstract

Background: Growing evidence supports improved survival with prehospital blood products. Recent trials show a benefit of prehospital tranexamic acid (TXA) administration in select subgroups. Our objective was to determine if receiving prehospital packed red blood cells (pRBC) in addition to TXA improved survival in injured patients at risk of hemorrhage.

Methods: We performed a secondary analysis of all scene patients from the STAAMP trial. Patients were randomized to prehospital TXA or placebo. Some participating EMS services utilized pRBC. Four resuscitation groups resulted: TXA, pRBC, pRBC+TXA, and neither. Our primary outcome was 30-day mortality and secondary outcome was 24-hour mortality. Cox regression tested the association between resuscitation group and mortality while adjusting for confounders.

Results: A total of 763 patients were included. Patients receiving prehospital blood had higher injury severity scores in the pRBC (22 [10, 34]) and pRBC+TXA (22 [17, 36]) groups than the TXA (12 [5, 21]) and neither (10 [4, 20]) groups ($p<0.01$). Mortality at 30 days was greatest in the pRBC+TXA and pRBC groups at 18.2% and 28.6% compared to the TXA only and neither groups at 6.6% and 7.4% respectively. Resuscitation with pRBC+TXA was associated with a 35% reduction in relative hazards of 30-day mortality compared to neither (HR 0.65; 95%CI 0.45–0.94, $p=0.02$). No survival benefit was observed in 24-hour mortality for pRBC+TXA, but pRBC alone was associated with a 61% reduction in relative hazards of 24h mortality compared to neither (HR 0.39; 95%CI 0.17–0.88, $p=0.02$).

Conclusions: For injured patients at risk of hemorrhage, prehospital pRBC+TXA is associated with reduced 30-day mortality. Use of pRBC transfusion alone was associated with a reduction in early mortality. Potential synergy appeared only in longer term mortality and further work to investigate mechanisms of this therapeutic benefit is needed to optimize the prehospital resuscitation of trauma patients.

Level of Evidence: Therapeutic, Level III

Keywords

Tranexamic acid; Prehospital; Blood; Mortality; Resuscitation

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BACKGROUND

Hemorrhage is the leading cause of early preventable death after injury. Minimizing time to resuscitation is critical to curtail early mortality and improve long-term survival.[1] Death from hemorrhage often occurs within the first few hours from time of injury and one-third of exsanguinating deaths occur prehospital.[1, 2] Damage control resuscitation has become the standard in-hospital strategy; however, prehospital resuscitation is not optimized to mitigate hemorrhage. Prior literature demonstrates inflammation and coagulopathy ensue within minutes of injury underscoring the need for prompt and targeted resuscitation strategies in the field.[3, 4]

Crystalloid remains the most widely used resuscitation fluid in the prehospital setting due to its availability and durability. Blood product administration in the field is limited by storage challenges and cost. Recent progress adopts the tenets of damage control resuscitation, adding blood products and limiting large volume crystalloids in the field.[5–7] The benefits of prehospital blood product resuscitation were demonstrated in military practice[8–11] and confirmed to be safe and effective in civilian trauma for patients in hemorrhagic shock.[12–18]

Important resuscitative and hemostatic adjuncts including anti-fibrinolytics have emerged in advanced resuscitative strategies. Antifibrinolytics aid in hemostasis as demonstrated in elective surgical cases.[19] Trauma induced coagulopathy can manifest as a hyperfibrinolytic phenotype in some patients, and is associated with poor outcomes.[20, 21] Administration of tranexamic acid (TXA) reduces mortality in bleeding trauma patients when provided at the receiving hospital.[22] Extrapolating this data, subsequent guidelines incorporated TXA into prehospital resuscitation algorithms.[23, 24] Recent studies further demonstrate safety and efficacy in select prehospital populations and dosing regimens.[25, 26]

As prehospital resuscitation capabilities become more sophisticated, the impact of combining multiple advanced prehospital resuscitation strategies is unclear. We previously demonstrated combining prehospital pRBC and plasma had a greater mortality benefit than either alone among patients in hemorrhagic shock.[16] However, outcomes associated with the combination of prehospital TXA with other prehospital resuscitation products represents a knowledge gap. Our objective was to determine if receiving prehospital pRBC in addition to TXA reduced mortality in injured patients at risk of hemorrhage. We hypothesized the combination of pRBC and TXA will be associated with reduced mortality in this population.

METHODS

Trial Design

We conducted a secondary analysis of the Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) trial. The details of the STAAMP trial have been previously published.[25] Briefly, the STAAMP trial was a multicenter pragmatic double-blind placebo-controlled trial which randomized patients undergoing emergency medical services (EMS) transport after injury to receive a 1-gram TXA bolus or placebo in the prehospital setting. Patients receiving TXA were further randomized in-hospital to three dosing regimens, including an abbreviated regimen with additional placebo bolus and

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infusion, a standard regimen with placebo bolus and TXA infusion, and a repeat regimen with additional TXA bolus plus TXA infusion.

In the STAAMP trial, twenty-four EMS bases enrolled and transported patients to four level 1 trauma centers. Among these, 12 EMS bases (all air medical transport agencies), provided pRBC as standard of care for prehospital resuscitation when indications were met (Fig. 1). This configuration of EMS bases led to four prehospital resuscitation groups for purposes of this study: (1) patients receiving prehospital TXA (TXA only group), (2) patients receiving prehospital pRBC and placebo (pRBC only group), (3) patients receiving prehospital pRBC and TXA (pRBC+TXA group), and (4) patients receiving placebo only (Neither group). Of note, all EMS bases provided crystalloid resuscitation to the above four groups.

Study Population

Inclusion criteria for the STAAMP trial were patients with at least one episode of hypotension (systolic blood pressure <90mmHg) or tachycardia (heart rate >110 beats per minute) within 2 hours of injury. Patients were excluded for age older than 90 years or younger than 18 years, lack of intravenous or intraosseous access, isolated fall from standing, documented cervical cord injury, known prisoner or pregnancy, traumatic arrest of more than 5 minutes, penetrating brain injury, isolated drowning or hanging, objection to study voiced at scene, or wearing a STAAMP study opt-out bracelet.

For the current study, we restricted the study population to patients transported directly from the scene of injury. This was done as there was limited data available about resuscitation products and volumes received when initially transported to a referring hospital, which might introduce unmeasured confounding.

Statistical Analysis

The primary outcome was 30-day mortality. Given the potential influence of multiple downstream in-hospital factors that might obscure the impact of prehospital interventions on 30-day mortality, we also assessed a secondary outcome of 24-hour mortality, an endpoint more proximate to the interventions of interest. We used Cox proportional hazard regression to evaluate the association with mortality outcomes and the four prehospital resuscitation groups. The proportional hazards assumption was evaluated by testing for difference from a non-zero slope of Schoenfeld residuals, with a significant testing indicating violation of this assumption. The Neither group, receiving neither prehospital pRBC nor TXA, was used as the reference category for reporting hazard ratios. Based on the results from the original trial, receiving prehospital pRBC was a clear marker of more severe injury and not randomized as the TXA groups were. Thus, we calculated a propensity score that reflected the likelihood of receiving prehospital pRBC based on the protocols for administering prehospital pRBC (Fig. 1) and prehospital variables that potentially could influence this decision. This propensity score included age, injury severity score (ISS), mechanism of injury, prehospital systolic blood pressure, prehospital heart rate, prehospital Glasgow Coma Scale, prehospital time, prehospital intubation, prehospital crystalloid volume, and head, chest, and abdominal abbreviated injury scale (AIS). The propensity score was then used as a covariate in our models. This allowed us to mitigate selection bias, as well as limit

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the number of variables included in the model to prevent overfitting given the small sample and number of outcome events. Propensity score distributions were examined. We also performed a sensitivity analysis weighted for the maximal overlap in propensity scores (Supplemental Methods).

As the resuscitation groups were not randomized by design, in addition to the propensity to receive prehospital pRBC, we also adjusted the models for intensive care unit admission, emergent/urgent surgical procedures within 24 hours, and TXA in-hospital dose. TXA in-hospital dose was included as it was part of the treatment of interest; however, patients could receive a second bolus plus infusion, infusion alone, or no further in-hospital TXA, representing a potential confounder. Covariates were selected *a priori* based on clinically relevant predictors of mortality in trauma and retained in the final models if they changed the primary treatment effect of interest coefficient by >10%.[27] Multiple organ failure, defined by Denver criteria, was included as a covariate in the 30-day mortality model but not the 24-hour mortality model given that it is calculated after 24 hours. Robust variance estimators were used to account for clustering by site. To evaluate potential differential effects of the resuscitation groups on mortality outcomes, we also tested several interactions, including prehospital systolic blood pressure and heart rate, prehospital time, lactate level, ISS, and AIS for head, chest, and abdominal regions.

Data analysis was conducted using Stata v17MP (StataCorp; College Station, TX). Continuous data are presented as median (interquartile range [IQR]). Continuous data were compared using Wilcoxon rank-sum tests, and categorical data compared using Chi-square. Cox proportional hazard model discrimination was assessed using Harrell's C-statistic and global goodness-of-fit assessed using the Groennesby and Borgan test. All included variables met the proportional hazards assumption by evaluation with Schoenfeld residuals. The overall fraction of missing data was low at 1% and addressed using multiple imputation as described in the original trial. A two-tailed p value ≤0.05 was considered significant. The University of Pittsburgh Institutional Review Board approved this study. Reporting of this study follows the STROBE guidelines for cohort studies.

RESULTS

A total of 763 patients were included from the 903 patients in the original STAAMP trial. There were 350 (46%) patients in the TXA only group, 35 (5%) patients in the pRBC only group, 22 (3%) patients in the pRBC+TXA group, and 356 (46%) patients in the Neither group (Fig. 2). Patients in the pRBC only and pRBC+TXA groups were sicker with higher ISS, lower systolic blood pressure, and higher unadjusted 24-hour and 30-day mortality than patients in the TXA only or Neither groups (Table 1). The distribution of propensity scores among the four resuscitation treatment groups are shown in eFigure 1.

In the primary outcome model for 30-day mortality, resuscitation with pRBC+TXA was associated with a 35% relative decrease in the hazards of mortality compared to the Neither group (HR 0.65; 95%CI 0.45–0.94, p=0.02). There was no association between the hazards of 30-day mortality and resuscitation with TXA only or pRBC only when compared to the Neither group (Table 2). Model diagnostics demonstrated excellent discrimination with

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Harrell's C-statistic of 0.81, and acceptable calibration with non-significant Groennesby and Borgan test (p=0.324). The proportional hazards assumption was not violated (p=0.259). Analysis weighted towards maximal overlap of the propensity score demonstrated similar overall results (eTable 1).

In the secondary outcome model for 24-hour mortality, resuscitation with pRBC-only was associated with a 61% relative reduction in the hazards of mortality compared to the Neither group (HR 0.39; 95%CI 0.17–0.88, p=0.02). There was no association between the hazards of 24-hour mortality and resuscitation with TXA only or pRBC+TXA when compared to the Neither group (Table 3), although the pRBC+TXA group was associated with a strong reduction in the point estimate of 24-hour mortality hazards with a p-value of 0.06. Model diagnostics demonstrated good discrimination with Harrell's C-statistic of 0.72, and acceptable calibration with non-significant Groennesby and Borgan test (p=0.472). The proportional hazards assumption was not violated (p=0.181). Analysis weighted towards maximal overlap of the propensity score demonstrated similar overall results, although the pRBC+TXA group did reach statistical significance in the association with reduced hazards of 24-hour mortality (eTable 2).

Several variables were significant in interaction testing. The pRBC+TXA group had significant interactions with prehospital systolic blood pressure ($p<0.001$), lactate level ($p<0.001$), and AIS abdomen ($p<0.001$). All resuscitation groups had significant interactions with prehospital heart rate ($p\leq0.001$), AIS head ($p<0.001$), and AIS chest ($p\leq0.01$). Finally, the pRBC only and pRBC+TXA groups had significant interactions with prehospital time ($p<0.01$) and ISS ($p<0.001$). Overall, for the pRBC only and pRBC+TXA groups, patients with lower systolic blood pressure, higher heart rate, higher lactate, more severe anatomic injuries, and longer prehospital time derived greater mortality benefit than less severely injured patients receiving similar prehospital resuscitation.

DISCUSSION

We found that prehospital resuscitation with the combination of pRBC and TXA reduces the hazards of mortality at 30 days for injured patients at risk for hemorrhagic shock. Notably, there was no 30-day mortality benefit for patients that received either product in isolation. Additionally, resuscitation with pRBC alone was associated with reduced mortality at 24 hours, consistent with prior literature,[15] while no early benefit was shown for TXA alone. There was a strong point estimate association of reduced 24-hour hazards for the pRBC+TXA; however, the p-value was 0.06. This may reflect an underpowered analysis given the low numbers in this group, especially as our weighted sensitivity analysis showed the pRBC+TXA group to be significantly associated with a reduction in the hazards of 24-hour mortality.

Amidst the push of advanced resuscitative techniques into the prehospital setting, pRBCs are the most commonly available blood products, and almost exclusively through air medical transport agencies.[28] Prior reports demonstrate feasibility, safety[29] and a growing body of evidence supports a mortality benefit.[9, 14, 15, 30–32] This was initially demonstrated out of literature from recent military conflicts wherein improved survival was observed for severely

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injured patients that received advanced prehospital care including pRBC transfusion.[9, 30] More recent civilian-based studies demonstrated a reduction in early mortality as well as biochemical improvements in coagulopathy for those that received prehospital pRBC.[14] A large propensity-matched, single-center study matched severely injured patients that received prehospital pRBC to those that did not and, similarly, found a reduction in early mortality at 24 hours.[15]

Given the logistical challenges and relatively limited availability of prehospital blood products, it is important that we continue to pursue adjunctive hemostatic therapies. Tranexamic acid has greater shelf life than blood products and can be widely deployed in ground and air EMS agencies. Tranexamic acid impairs the biochemical conversion of plasminogen to plasmin, and at higher concentrations, inhibits plasmin, serving as potent adjunct in resuscitation efforts as an inhibitor of fibrinolysis.[33] Our finding of 30-day but not 24-hour survival benefit of adding prehospital TXA to pRBC in the main analysis could suggest its anti-fibrinolytic mechanism may not be the only property responsible for its effects in recent trials. Notably, plasmin carries proinflammatory effects by activating endothelium and platelets, and also has a role in innate immune signaling.[34, 35] Plasmin induces chemotaxis of monocytes and dendritic cells with release of proinflammatory cytokines.[35, 36] Thus, the benefit of TXA observed in the current study may be through inhibition of plasmin and attenuation of inflammation, ischemia-reperfusion, and complement activation.[37–40]

TXA effectively reduces surgical bleeding[19] and following the CRASH-2 trial[22], is increasingly utilized in prehospital care. This trial demonstrated a reduction in mortality from bleeding with early administration from time of injury at the receiving hospital, as compared to placebo, with the greatest benefit observed for those that received TXA within one hour of injury. Subsequently, the CRASH-3 trial compared TBI patients and in-hospital head-related mortality at 28 days for those that received in-hospital TXA within three hours of injury vs placebo. Although a negative trial for the primary outcome, head-related mortality was reduced in the TXA arm at 24-hours and in sensitivity analysis for those with mild to moderate TBI, without observed differences in vaso-occlusive or seizure events.[41] Morrison and colleagues thereafter conducted a retrospective military study comparing hospital TXA versus no TXA in combat injuries for patients requiring pRBCs. They also demonstrated improved survival for the most severely injured patients with an associated improvement in coagulopathy.[42]

Extrapolating this evidence to the field, EMS systems implemented TXA protocols[43, 44] and retrospective studies demonstrate reduced fibrinolysis, a safety profile marked by venous thromboembolism, mixed results on early outcomes, and a paucity of long-term data.[23, 45, 46] The STAAMP trial addressed this evidence gap and showed a reduction in mortality in patients with TXA ≤ 1 hour, 3-gram total dose, and those with SBP ≤ 70 mmHg, with no differences in seizure or thrombotic complications.[25] In another secondary analysis of STAAMP, for patients at greatest risk of hemorrhage, receipt of early TXA ≤ 1 hour was associated with a reduction in 30-day mortality risk.[47] A prehospital trial by Rowell et al. investigated the impact of prehospital TXA on long term neurologic function for patients with TBI.[26] The authors found no difference in 6-month neurologic outcomes; however,

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there was lower 28-day mortality among patients that received a 2-gram bolus only dosing regimen.

Taken together, the current body of literature indicates that TXA is safe and effective but should be administered in appropriately selected patient cohorts as evidenced by the subgroup analyses of several of these trials.[22, 25, 41] In the present study, we demonstrate the best outcomes for patients that received combined therapy with pRBC and TXA transfusion and similar to the original trial, the greatest benefit is observed for those most severely injured with severe shock and high ISS. A secondary analysis of the PAMPer trial also corroborates best outcomes for patients receiving combination prehospital therapies.[13] Severely injured patients in hemorrhagic shock who received combined prehospital pRBC and plasma showed the greatest mortality benefit.[16]

Trauma and severe shock cause early coagulopathy, endotheliopathy, and systemic inflammation that is difficult to reverse.[48] Our findings have important implications for improving the prehospital phase of trauma care. Optimal management requires prehospital, early, and multi-modal resuscitation to ameliorate the complex pathophysiologic insult of injury. Early prehospital use of TXA may benefit patients who require prehospital pRBC resuscitation. Future investigations should aim to delineate the mechanisms responsible for combined resuscitation strategy benefits, as well as further define the injured patient populations most likely to benefit from prehospital TXA. The PATCH multicenter trial is currently underway and evaluates prehospital TXA in severe trauma.[49, 50] Results of this trial will supplement the available evidence as we work to improve prehospital care of trauma patients at risk of exsanguination.

This study has several important limitations to acknowledge. First, this was a secondary analysis of a randomized trial with a hypothesis that differed from that of the original design. This resulted in relatively small sample sizes within our defined resuscitation groups. In particular, there were only 22 patients in the pRBC+TXA group, potentially making some of our analyses underpowered to find an effect, again such as no association with 24-hour mortality. Efforts to explore sensitivity analyses and better elucidate significant interactions led to unstable models. Additionally, the majority of our patients sustained blunt trauma and were treated in mature trauma systems of four participating trauma centers by trial protocol. This may limit the generalizability of our findings for those with penetrating injury or patients served in differing trauma systems without access to advanced prehospital resuscitation. As noted, prehospital pRBC are limited in availability currently, although advances such as freeze-dried products may make prehospital blood products more readily available.

CONCLUSION

For injured patients at risk of hemorrhage, prehospital resuscitation with a combination of pRBC and TXA is associated with a reduction in the risk of 30-day mortality. Prehospital pRBC transfusion alone was associated with a reduction in the risk of early mortality. Prehospital professionals with the capability to provide both pRBC and TXA should consider administering TXA to any patient meeting criteria for prehospital pRBC

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transfusion. Potential synergy appeared most robustly in longer term mortality and further work to investigate mechanisms of this therapeutic benefit is needed to optimize the prehospital resuscitation of trauma patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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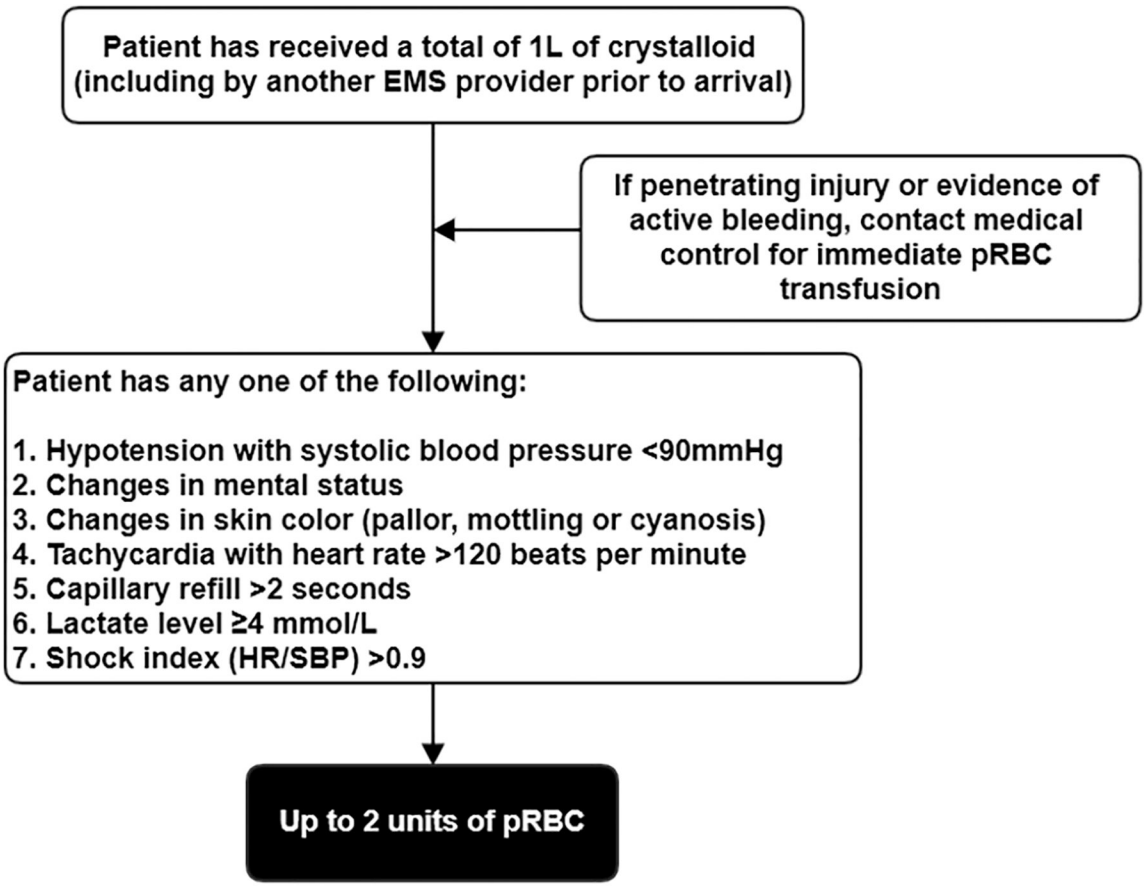

Figure 1.
Emergency medical services protocol for prehospital pRBC transfusion on scene.

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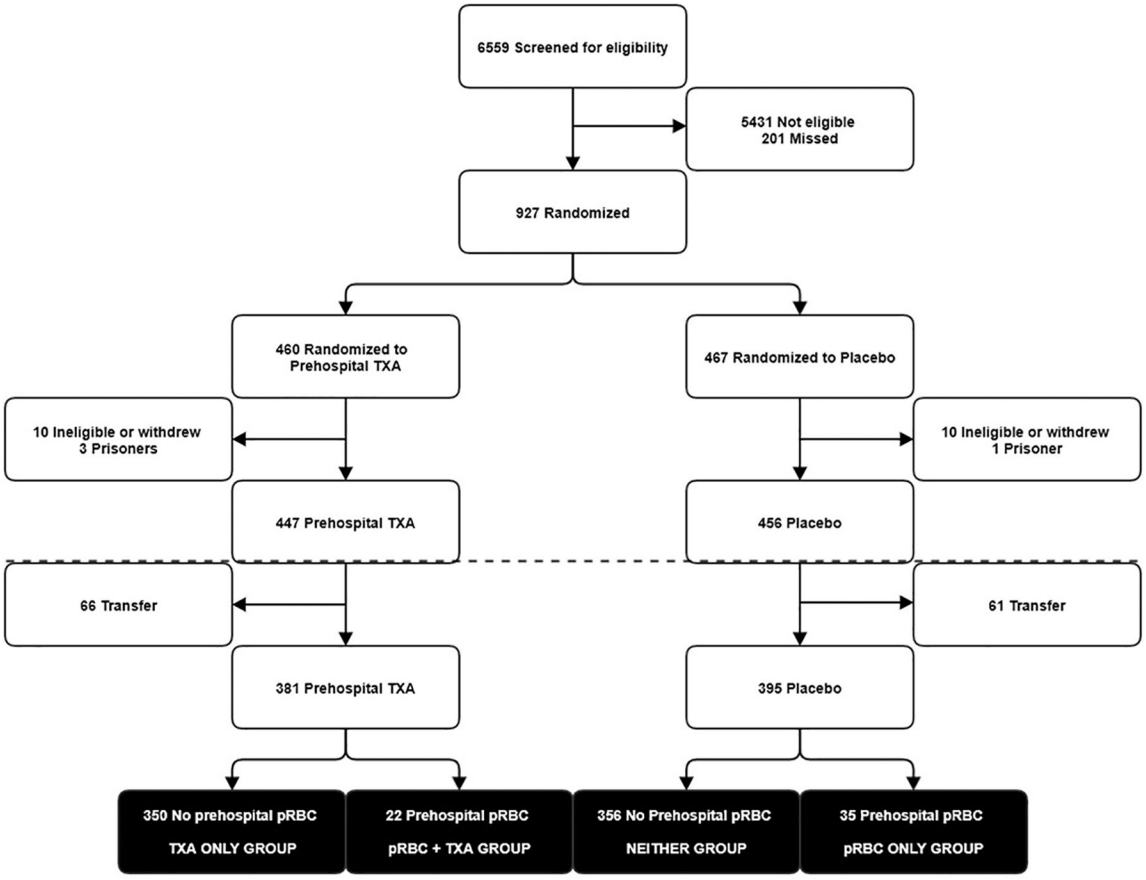

Figure 2.

Study participant selection and resuscitation groups from the Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) trial. Participant selection below dotted line indicates cohort selection beyond the original trial population for this study.

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Table 1.

Patient Characteristics by Resuscitation Group

	TXA (n=350)	pRBC (n=35)	TXA + pRBC (n=22)	Neither (n=356)	p-value
Age, years	39 (26, 52)	53 (40, 69)	39 (31, 56)	37 (25, 55)	<0.001
Sex (male)	254 (73%)	23 (66%)	11 (50%)	262 (74%)	0.090
Blunt mechanism	305 (87%)	28 (80%)	18 (82%)	323 (91%)	0.130
PH time, min	37 (28, 46)	41 (31, 63)	41 (34, 49)	36 (30, 45)	0.068
PH SBP, mmHg	128 (90, 147)	84 (74, 95)	86 (68, 102)	128 (89, 148)	<0.001
PH HR, bpm	118 (112, 128)	112 (90, 120)	115 (99, 140)	118 (112, 125)	0.074
PH GCS	14 (12, 15)	13 (3, 15)	15 (8, 15)	14 (12, 15)	0.120
PH crystalloid, mL	400 (110, 850)	1000 (700, 2000)	910 (300, 1400)	400 (0, 750)	<0.001
PH intubation	81 (23.1%)	17 (48.6%)	9 (40.9%)	85 (23.9%)	0.003
ED SBP, mmHg	130 (110, 144)	98 (82, 108)	95 (88, 110)	132 (110, 150)	<0.001
ED HR, bpm	105 (91, 117)	101 (89, 113)	109.5 (89, 129)	106 (91, 120)	0.590
ED GCS	15 (11, 15)	11 (3, 15)	12.5 (3, 15)	15 (10, 15)	0.003
ISS	12 (5, 21)	22 (10, 34)	22 (17, 36)	10 (4, 20)	<0.001
24-hour pRBC, units	0 (0, 0)	5 (1, 11)	5 (2, 10)	0 (0, 0)	<0.001
24-hour plasma, units	0 (0, 0)	2 (0, 7)	0 (0, 5)	0 (0, 0)	<0.001
24-hour crystalloid, mL	2650 (1100, 5000)	6048 (3900, 7729)	4663 (2000, 7600)	2434 (1010, 4925)	<0.001
MOF	24 (7%)	9 (26%)	4 (18%)	26 (7%)	<0.001
3-hour mortality	5 (1%)	3 (9%)	1 (5%)	4 (1%)	0.007
6-hour mortality	8 (2%)	3 (9%)	1 (5%)	6 (2%)	0.066
24-hour mortality	10 (3%)	5 (14%)	3 (14%)	9 (3%)	<0.001
30-day mortality	24 (7%)	10 (30%)	4 (19%)	24 (7%)	<0.001

Continuous variables presented as median (IQR)

Categorical variables presented as n (%)

TXA, tranexamic acid; pRBC, packed red blood cells; PH, prehospital; SBP, systolic blood pressure; HR, heart rate; ED, emergency department; ISS, injury severity score; MOF, multiple organ failure

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Table 2.

Cox proportional hazard regression resuscitation group results for 30-day mortality

	Hazard Ratio	95% Confidence Interval	p-value
Resuscitation group			
Neither	Reference	-	-
TXA only	0.99	0.39 – 2.51	0.986
pRBC only	1.05	0.57 – 2.00	0.842
pRBC+TXA	0.65	0.45 – 0.94	0.022
ICU admission	1.13	0.75 – 1.69	0.552
MOF	1.95	1.38 – 2.75	<0.001
Urgent procedure	1.24	1.17 – 1.33	<0.001
TXA dose	0.96	0.74 – 1.24	0.768
Propensity Score	76.67	50.43 – 122.72	<0.001

TXA, tranexamic acid; pRBC, packed red blood cells; ICU, intensive care unit; MOF, multiple organ failure

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Table 3.

Cox proportional hazard regression resuscitation group results for 24-hour mortality

	Hazard Ratio	95% Confidence Interval	p-value
Resuscitation group			
Neither	Reference	-	-
TXA only	1.00	0.71 – 1.40	0.990
pRBC only	0.39	0.17 – 0.88	0.024
pRBC+TXA	0.33	0.10 – 1.08	0.068
ICU admission	0.11	0.06 – 0.20	<0.001
Urgent procedure	1.58	0.89 – 2.81	0.081
TXA dose	0.97	0.60 – 1.58	0.916
Propensity Score	991.57	475.57 – 2067.46	<0.001

TXA, tranexamic acid; pRBC, packed red blood cells; ICU, intensive care unit